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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,776	05/05/2005	Rainer Albert	TX/4-32662A	5246

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EXAMINER	
BALLS, ROBERT J	

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 11/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/529,776	ALBERT ET AL.	
	Examiner	Art Unit	
	R. James Balls	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-8 are pending.

2. This application is a 371 of PCT/EP02/10226 filed on September 12, 2002.

3. Claims 1-8 to the extent they are drawn to compounds wherein R2 is either phenyl or pyridine are currently under examination.

Election/Restrictions

4. Applicants' election with traverse of Group I in the reply filed on August 23, 2006 is acknowledged. Applicants traverse the restriction alleging that when all compounds share a common structure, restriction is improper under the PCT rules. This is not found persuasive because the common structural feature must make a contribution over the prior art (i.e. be novel and/or non-obvious). See Annex B Part 1(b). In the instant case, all compounds share a common structure (the bicyclic piperadine core). However, the common structure does not make a contribution over the prior art (it either lack novelty or is an obvious variation). See McCombie et al. (WO/0066559), cited in the previous requirement for restriction.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112, Second Paragraph
35 USC §101

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claim 5 provides for the use of a compound but does not set forth any steps involved in the method/process. Therefore, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. See MPEP 2173.05(q).

6. Claim 5 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 7-8 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The claims are drawn to a method of "preventing" or

treating disorder or diseases "mediated" by interactions between chemokine receptors and their ligands in patients in need thereof. The terms, "preventing" and "mediated" render the claim indefinite. The claim is drawn to treating a patient in need of such treatment, i.e. a patient with a disease or disorder. It is inconsistent to use the term, "prevent," because a patient in need thereof already has the disease or disorder and therefor is in need of treatment not prevention. The term "mediated" renders the claim indefinite because it does not clearly identify the relationship between diseases or disorder and chemokine receptors and their ligands. For instance, the term "mediated" may include both activation and deactivation or a receptor's activity. The claim is drawn to diseases mediated by *interactions* between chemokine receptors and their ligands." The word "interaction" is a relative term of degree, which doesn't describe any cause-effect relationship. There is no explanation as to how the ligand and receptor interact and for what purpose they interact. Thereby, failing to appraise one skilled in the art of the metes and bound of patent protection sought.

Claim Rejections - 35 USC § 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-5 are rejected under 35 U.S.C. §103(a) as being unpatentable over Albert et al. (WO 02/081449) in view of Baroudy et al. (WO 00/66559).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Both Albert et al. and Baroudy et al. are drawn to analogous art, i.e. dipiperadine derivatives useable as CCR5 antagonists. Albert et al. requires a disubstituted amino group attach to the dipiperadine core (the left side of formula 1). Baroudy et al. requires -C(O)- attach to the nitrogen of the dipiperadine core (the right side of formula 1).

Ascertainment of the Difference Between the Prior Art and the Claims (MPEP §2141.02)

The instant claims differ from Albert et al. by requiring a particular subgenus of Albert et al. Albert et al. allows Y to be a variety of different groups including -C(O)- whereas the instant claims provide only the -C(O)- group.

The instant claims differ from Baroudy et al. by requiring a particular subgenus of Baroudy et al. Baroudy et al. discloses compounds with both a disubstituted amino and a disubstituted methyl group linked to the dipiperadine core whereas the instant claims require only a disubstituted amino group.

Motivation and Prima Facie Obviousness-Rationale (MPEP §§2142-2143)

One of ordinary skill in the art would be motivated to make compounds of the instant claims because Albert et al. motivates the skilled artisan to use a disubstituted amino group (on the left side of the dipiperadine structure) and Baroudy et al. motivates the skilled artisan to use a -C(O)- (on the right side of the structure). See Albert et al. page 1, formula 1 and the corresponding species disclosed in the specification. See Baroudy et al., page 2, formula 1 and the corresponding species. For example, compare Albert et al., page 22, Examples 76 with Baroudy et al.,page 63 Example 11A. By combining the left side of the Albert et al. compound (Example 76) with the right side of the Baroudy et al. compound (Example 11A) the skilled artisan arrives at the compound of Example 1 of the instant application. Therefore, it would be obvious to the skilled artisan, in possession of these references, to arrive at the invention of the instant claims with a reasonable expectation of success.

The applied reference (Albert et al.) has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed

subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Claim Rejections - 35 USC § 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-5 are rejected under 35 U.S.C. §103(a) as being unpatentable over Baroudy et al. (WO 00/66559) in view of Asberom et al. (WO 98/01425).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Both Baroudy et al. and Asberom et al. are drawn to analogous art, i.e. dipiperadine derivatives useable as CCR5 antagonists. Baroudy et al. provides compounds having a disubstituted methyl group linked to the dipiperadine core. See examples 11-13. Asberom et al. provides compounds with a disubstited amino group linked to the core. See Example 5 and the definitions for R1 in Claim 1.

Ascertainment of the Difference Between the Prior Art and the Claims (MPEP §2141.02)

Baroudy et al. provided for a disubstitued methyl group whereas the instant claims require a disubstituted amino group. For example see Baroudy et al., compound 11A on page 63.

Asberom et al. is drawn to a broader genus than the instant claims. Not all compounds encompassed by Asberom et al. require a dipiperadine core.

Motivation and Prima Facie Obviousness-Rationale (MPEP §§2142-2143)

One of ordinary skill in the art would be motivated to make compounds of the instant claims because the disubstituted methyl group of Baroudy et al. is interchangeable with disubstituted amino groups as evidenced by Baroudy et al. The amino substitutions, phenyl, pyridyl, and benzyl are generically provided by Baroudy et al. and Asberom et al. provides benzyl and methylpyridine substitutents. For example, see the exemplified compounds of Baroudy et al, which have R3 as benzyl, methylpyridyl (for benzyl, see Example 13). Therefore, one of ordinary skill in the art would recognize that the disubstituted methyl group can be exchanged for a disubstituted amino group and expect the resulting compounds to have similar activity.

Double Patenting

10. Claims 1-4 and 6 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of copending application Serial No. 10/472,653 (US 20040142920) in view of Baroudy et al. (WO 00/66559). Although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons given above in section 8, which is incorporated herein in its entirety. (Application Serial No. 10/472,653 is the national stage of Albert et al. (WO 02/081449)).

Furthermore, the instant claims differ from the copending application's claims by reciting a more limited genus. The copending application allows Y to be a variety of different groups including -C(O)- whereas the instant claims provide only the -C(O)- group linked to the ring nitrogen of piperadine. It would have been obvious to one

having ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the copending application, including those of the instant claims, because an ordinary artisan would have the reasonable expectation that any of the species of the genus would have similar properties and the same use as the genus as a whole. In this case, it would have been particularly obvious to choose Y = -C(O)- based the copending claims (see Claim 5) guided by the examples 1-40, and 43-83 (all but two), which have the -C(O)- group for Y.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112, Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 7-8 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. An adequate written description "guards against the inventor's overreaching by later claiming that which he did not invent, by insisting that he recount his invention in such detail that his future claims can be determined to

be encompassed within his original creation." *Vas-Cath v. Mahurkar*, 935 F.2d at 1561 (Fed.Cir. 1991).

Claim 8 is drawn to a method for treating disorders or diseases mediated by interactions between chemokine receptors and their ligands. The claim encompasses diseases, chemokine receptors and ligands known at the time of application filing as well as diseases, chemokine receptors and ligands not yet discovered. Claim 9 further requires a "second drug substance." Again, the term "second drug substance" includes all drug substances known at the time of filing and substances discovered thereafter.

A positive delineation of the contents of these terms (chemokine receptors, ligands, diseases, and second drug substances) are not found and representative species are not shown. Therefore, the claim reaches through to future diseases, receptors, ligands and substances not yet known or discovered. This broad scope would give applicants patent protection extending beyond that which is described in the specification, known in the art, or possessed by applicants in violation of 35 U.S.C. §112. For a more detailed explanation and commentary on reach-through claims, see LeCointe, *Reach-Through Claims*, INTERNATIONAL PHARMACEUTICAL (2002) (also available at: http://www.bakerbotts.com/infocenter/publications/detail.aspx?id=bffe4a7d-5beb-4cf8-a189-15a5f190f0eb) and Silva, *Reach Through Claims: Bust or Boon?*, INTELLECTUAL PROPERTY UPDATE (available at: http://www.dorsey.com/publications/legal_detail.aspx?FlashNavID=pubs_legal&pubid=170565003).

Claim Rejections - 35 USC § 112, Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 7-8 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916), where the Supreme Court looked to whether the experimentation needed to practice an invention was undue or unreasonable. *Id.* An invention must be described so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). Courts rely on the following factors set out in *In re Wands* to determine whether undue experimentation is required to practice a claimed invention:

(a) The breadth of the claims;
(b) The nature of the invention and predictability in the art;
(c) The state of the prior art;
(d) The level of one of ordinary skill;
(e) The existence of working examples; and
(f) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The analysis is applied to the instant case.

(a) The claims are broad as they are drawn to a method for treating any and all chemokine mediated disease.

(b) The invention is physiological in nature as it is directed toward pharmaceuticals and treating diseases with those pharmaceuticals, an art which is highly unpredictable. "[T]he scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). In the highly unpredictable pharmaceutical art, the required disclosure is greater than for the disclosure of an invention involving predictable factors such as mechanical or electrical elements. *In re Vaeck*, 20 USPQ 2d 1438 (CAFC 1991).

(c) The state of the chemokine receptor art is highly unpredictable. For example, Cohen et al. explains, "The mode of action of many of the cytokines involves typical signal transduction events such as protein phosphorylation, and to date there is only limited understanding of the mechanisms that lead to one activity over another when a specific cytokine is involved in a specific biological reaction." Cohen et al., AM. J. CLIN. PATHOL., 1996, 105, 589.

(d) The level of skill required to practice the invention is high due to its pharmaceutical nature.

(e) The amount of guidance and working examples in the specification is limited to in vitro binding activity. The last few pages of the specification (there are no page numbers) provides a CCR5 membrane binding assay, A CCR5 Functional Assay-CA2+

Mobilization, and a CCR5 Functional Assay – Chemotaxis. Although these assays demonstrate the compounds ability to interact with CCR5, there is no evidence that any of the compounds are capable of treating or preventing any and all disorders "mediated by interactions between chemokine receptors and their ligands."

(f) The quantity of experimentation necessary to make or use the disclosed invention is high, based on the unpredictability of the art, the limited guidance in the specification, and the lack of direction and working examples.

In view of the high degree of unpredictability with regard to cytokine biological activity and the assay data showing only in vitro CCR5 activity, the specification has not offered guidance for a method of treating chemokine mediated diseases sufficient to avoid immense and undue experimentation

Notice of Related Art

13. Palani et al. (US 2004/0010008) provides compounds similar to applicants' claimed compounds. Claim 1 of Palani et al. reads on the instant claims. The priority date of Palani et al. is August 29, 2001. The priority date of the instant claims is October 7, 2002. An obviousness rejection has not been made at this time because the exemplified compounds of Palani et al. have R2 as a pyrimidine ring, a substitution not currently under examination (drawn to non-elected subject matter).

Conclusion

14. No claims are allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to R. James Balls whose telephone number is (571) 272-7997. The examiner can normally be reached on Mon - Fri 8:00am - 4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tom McKenzie can be reached on (571) 272-0670. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

R. James Balls
October 24, 2006

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Art Unit 1625